REMARKS

Status of the Claims

After entry of the instant Amendment, claims 1, 2, 4-7, 9-24, 27, 34-37 and 39-48 are pending in the present application. Claims 5, 7, 9-24, 27, 35 and 37 are withdrawn from consideration as being drawn to non-elected inventions. Claims 8 and 38 have been cancelled and claims 1, 2, 4, 6, 34 and 36 have been amended without prejudice or disclaimer of the subject matter contained therein. New claims 39-48 have been added.

Independent claims 1 and 2 have been amended as suggested by the Examiner to recite a NOD/SCID/IL2rg-null mouse, and dependent claims 4, 6, 34 and 36 have been amended to be consistent with the amendments to claims 1 and 2. Support for new claims 39-44 can be found at least at page 31, line 8 to page 32, line 12; Table 3 at page 28; and Figure 11 of the present Specification. Support for new claim 45 can at least be found at page 9, ll. 18-22 and page 24, ll. 4-7 of the present Specification. Support for new claims 46-48 can at least be found at page 11, ll. 7-10, and Table 2 at page 26 of the present Specification.

No new matter has been added by way of amendments to the claims. Reconsideration of this application, as amended, is respectfully requested.

Priority Under 35 U.S.C. § 119

Applicants are filing a certified copy of an English translation of Japanese Patent Application JP-2003-171240 herewith. Applicants respectfully request that the Examiner acknowledge Applicants' claim for foreign priority to JP-2003-171240 under 35 U.S.C. § 119 and receipt of the certified priority document in the next Office Action.

Claim Objections

Claims 1, 2, 4-8, 34, 36 and 38 have been objected to for the recitation of a "SCID/IL2rg-null mammal (excluding human)." Claims 8 and 38 have been cancelled and their rejections are therefore moot. Claim 7 is withdrawn. Applicants have amended independent claims 1 and 2 to recite a NOD/SCID/IL2rg-null mouse, as suggested by the Examiner, to overcome the objection. Claims 4, 6, 34 and 36 depend (directly or indirectly) from amended claims 1 and 2, and have been amended to be consistent with the amendments made to claims 1 and 2. In view of the

discussion above, Applicants respectfully request that the objections to claims 1, 2, 4, 6, 34 and 36 be withdrawn.

Rejections Under 35 U.S.C. § 112, New Matter/Written Description

Claims 1, 2, 4, 6, 8, 34, 36 and 38 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and for introducing new matter. Claims 8 and 38 have been cancelled and there rejection is now moot. Rejection of claims 1, 2, 4, 6, 34 and 36 is respectfully traversed.

In the Office Action it is alleged that the claims contain subject matter (*e.g.*, SCID/IL2rg-null non-human mammals) that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, that the Inventors, at the time the application was filed, had possession of the claimed invention, and that the recitation in the claims of a "SCID/IL2rg-null mammal (excluding human)" introduces new matter.

It is conceded in the Office Action that a NOD/SCID/IL2rg-null mouse is disclosed in the Specification and that the Applicants were in possession of the same at the time the application was filed. As discussed above, claims 1, 2, 4, 6, 34 and 36 now recite a NOD/SCID/IL2rg-null mouse, as suggested by the Examiner. Thus, Applicants respectfully submit that the claims, as amended, comply with the enablement and written description requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 4, 5, 8, 34 and 38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishikawa et al., Exp. Hematol. 30(5):488-494; May 2002 (hereinafter "Ishikawa"), in view of mouse strain NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz (Stock No: 005557, Jackson Laboratory) (hereinafter "mouse strain 005557").

Claims 1, 2, 6 and 36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishikawa, in view of mouse strain 005557, as applied to claims 1, 2, 4, 5, 8, 34, 35 and 38 above, and further in view of Olive et al., Immunol., Cell Biology, Vol. 76, pp. 520-525, 1998.

Applicants assume that the citation of the Ishikawa reference in the Office Action was incorrect, and this response is being made based on the assumption that the Examiner meant to cite Ishikawa et al., Exp. Hematol. 30(5):488-494; May 2002. Ishikawa is not an author of the article in Am. J. Transpl. vol. 2, pp. 520-525, 2002, as cited in the Office Action. Also, the mouse strain is cited in the Office Action as having a Jackson Lab stock number of 00557 (which is not a SCID mouse strain), therefore Applicants assume the Examiner meant to refer to stock number 005557 (which is a SCID mouse strain).

The mouse strain 005557 cited in the Office Action was not developed until 2005, after the priority date of the claimed invention. (*See* article and catalog information attached.) Thus, mouse strain 005557 is not prior art. It is not clear from the product description for mouse strain 005557 that it had been published at the time the claimed invention was made.

Ishikawa and Olive taken alone or together do not teach NOD/SCID/IL2rg-null mice, as in the claimed invention, and mouse strain 005557 is not prior art. Therefore, in view of the discussion above and the documents attached, Applicants respectfully request that the rejection of claims 1, 2, 4, 6, 34 and 36 as being unpatentable over Ishikawa in view of mouse strain 005557 (and further in view of Olive for claims 1, 2, 4, 5, 34 and 35) be withdrawn.

New Claims

Applicants would like to point out that claims 39-44 recite "antigen-specific human IgG, IgM and IgA" or "the amount of antigen-specific human IgG in the serum of the mouse." None of the cited art references (Ishikawa, Olive, or mouse strain 005557) teach the generation of antigen-specific immunoglobulins, as recited in claims 39-44.

Claim 45 is drawn to a method of producing a NOD/SCID/IL2rg-null mouse transplanted with human-derived hematopoietic stem or precursor cells, wherein the method comprises irradiating an immature NOD/SCID/IL2rg-null mouse, and transplanting human-derived hematopoietic precursor cells or mature hematopoietic cells into the irradiated mouse. Ishikawa teaches away from engrafting human cells into NOD/SCID mice, where the mice are conditioned using irradiation prior to introduction of human-derived hematopoietic stem or precursor cells.

Claims 46-48 recite ratios of human-derived antibody- generating cells to recipient-derived antibody-generating cells in various tissues of the claimed mice. Ishikawa teaches that

NOD/SCID/β2-microglobulin^{null} mice show better engraftment than NOD/SCID mice. Therefore, based on the teachings of Ishikawa, it is unexpected that Examples in the present Specification comparing the engraftment levels of NOD/SCID/β2-microglobulin^{null} mice with the inventive NOD/SCID/IL2rg-null mouse strain, the engraftment levels for the inventive strain appear to be much higher. (See Table 2 at page 26.)

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Stephanie A. Wardwell, Ph.D., Registration No. 48,025, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: February 24, 2010

Respectfully submitted,

By _____
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Attachments: Jackson Laboratory catalog description of stock number 005557
"A New Model for Engraftment with Human Hematopoietic Stem Cells," JAX Notes, Issue 498, Summer 2005 (5 pages)
English translation of Japanese Patent Application JP-2003-171240 (23 pages)

A New Model for Engraftment with Human Hematopoietic Stem Cells

JAX® NOTES Issue 498, Summer 2005

A new mouse model that can support a human immune system was recently developed by The Jackson Laboratory's Dr. Leonard Shultz and collaborators at St. Jude Children's Research Hospital and the University of Tennessee, both in Memphis, the EMD Lexigen Research Center, Billerica, Massachusetts, and the University of Massachusetts, Worcester. The mouse will allow scientists to 1) perform the critical studies necessary to improve hematopoietic stem cell (HSC) transplants for treating leukemia, sickle cell disease, and other blood disorders (all without putting patients at risk), and 2) study the HIV(AIDS) virus in a model that mimics the human immune system better than any previously constructed.

The model, NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/Sz, combines the features of the NOD/LtJ (Stock Number 001976) background, the severe combined immune deficiency mutation (*scid*, which is caused by a spontaneous mutation of the *Prkdc* gene), and *Il2rg*-deficiency. It is deficient in mature lymphocytes and natural killer (NK) cells. *Il2rg* is indispensable for IL2, IL4, IL7, IL9, IL15, and IL21 high affinity binding and signaling. In mice, it is also thought to play a key role in mediating susceptibility to thymic lymphomas. In humans, IL2RG-chain deficiency causes X-linked SCID, blocks Nk cell development, and results in additional defects in innate immunity.[1]

NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/Sz has two major advantages over previous immunodeficient mouse models. First, because it is resistant to lymphomas (even after sublethal irradiation), it lives for over 16 months. Its longevity is particularly important because it will enable researchers to conduct long-term experiments not possible with previous immunodeficient mice. Second, although the *scid*, *B2m*-deficient, *Rag1*-deficient, and *Rag1-Pfr*-deficient mice on the NOD/LtJ background we compare[2] in a previous issue of JAX Notes™ have been successively better in their ability to engraft human HSCs, they fail to differentiate those HSCs into mature human lymphoid and myeloid cells. In contrast, the bone marrow of HSC-engrafted *Il2rg*-deficient mice generates six times more human CD45+ cells (B cells, NK cells, myeloid cells, plasmacytoid dendritic cells, and HSC) than does the bone marrow of similarly treated NOD.CB17-*Prkdc*^{scid}/J mice. Their spleens contain functioning human *Ig*$^{+}$ B and T cells (CD3+). Co-administering human Fc-IL7 fusion protein along with HSCs results in high percentages of human CD4+CD8+ thymocytes and human CD4+CD8- and CD4-CD8+ peripheral blood and splenic T cells.

Because the *Prkdc*^{scid} *Il2rg*^{tm1Wjl} model has such a superior ability to engraft human hematopoietic stem cells (HSCs) and differentiate them into the various cell subsets of the human immune system, it will be capable of acting as a surrogate for the human immune system and thus enable researchers to avoid the complex ethical issues of conducting research directly in humans. Essentially, researchers will be able to produce a human immune system in a mouse. As Dr. Rupert Handgretinger, director of stem cell transplantation at St. Jude and co-leader of the Transplantation and Gene Therapy Program says: "Hematopoietic stem cell transplantation to replace a patient's own blood system could cure many more people who have blood cancers and certain genetic and immune disorders. Unfortunately, this treatment has not reached its full potential, in part because of ethical limitations on studying stem cell transplantations in humans. Our new laboratory model will now let researchers around the world do many important experiments that will provide valuable insights into how the immune system works and how to increase the success rate of HSC transplantation."[3] The model will be a valuable tool for studying how stem cells give rise to the various cells of the immune system, how immune cells kill cancer cells and fight infections, and how immune cells respond to radiation and chemotherapy, two major treatments for many cancers. Dr. Shultz of The Jackson Laboratory is very enthusiastic about the model's potential: "Because this new humanized mouse model will permit studies of normal stem cell function, it will be a very important tool in research on regenerative medicine. The ability of these mice to support development of a functional human immune system should also facilitate the testing of experimental human vaccines and help us understand the mechanisms underlying human autoimmune diseases."[3]

The new model should also firmly establish the inbred mouse's niche in HIV(AIDS) research. Although mice are biologically similar to humans, the native mouse immune system is not susceptible to HIV. The ability of this mouse model to support a fully functional human immune system will solve that problem.

References:

(Authors in **bold** are Jackson Laboratory scientists)

[1]**Shultz LD**, Lyons BL, Burzenski LM, Gott B, Chen X, Chaleff S, Kotb M, Gillies SD, King M, Mangada J, Greiner DL, Handgretinger R. 2005. Human lymphoid and myeloid cell development in NOD/LtSz-scid IL2Rgnull mice engrafted with mobilized human hemopoietic stem cells. *J Immunol* 15:6477-89.

[2]JAX Notes™. 2005. NOD.Cg-*Rag1*^{tm1Mom} *Prf1*^{tm1Sdz}/SzJ, a new immunodeficient mouse strain supporting enhanced human hematolymphoid cell engraftment. *JAX Notes™* 496:10.

[3]St. Jude Children's Research Hospital. 2005. Laboratory model of immune system overcomes ethical constraints on studies of

hematopoietic stem cells in humans. St. Jude Children's Research Hospital news release May 9, 2005 (www.stjude.org/news).

The Jackson Laboratory
Leading the search for tomorrow's cures

Strain Name: NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ

Stock Number: 005557

Availability: Level 2

Use Restrictions Apply, see ***Terms of Use***

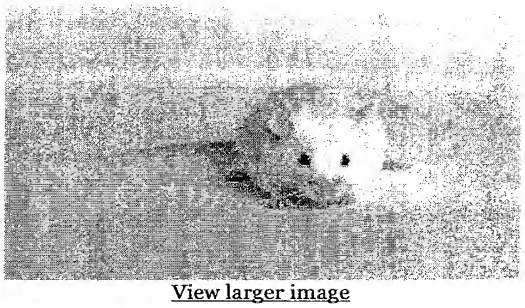
Common Names: NOD scid gamma; NSG; NOD-scid IL2Rgamma^{null}; NOD-scid IL2Rg^{null};

These mutant mice combine the features of the NOD/ShiLtJ background, the severe combined immune deficiency mutation (*scid*) and IL2 receptor gamma chain deficiency. As a result, the NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice lack mature T cells, B cells, or functional NK cells, and are deficient in cytokine signaling, leading to better engraftment of human hematopoietic stem cells and peripheral-blood mononuclear cells than any other published mouse strain. Recent publications have demonstrated this strain's outstanding utility in the studies of islet transplantation, hematopoietic stem cells and cancer stem cells.

Description

Strain Information

Type	Congenic; Mutant Strain; Spontaneous Mutation; Targeted Mutation; Additional information on Genetically Engineered and Mutant Mice. Visit our online *Nomenclature tutorial*. Additional information on *Congenic nomenclature*.
Mating System	Homozygote x Homozygote (Female x Male) 01-MAR-06
Species	laboratory mouse
H2 Haplotype	*g7*
Generation	N8F?+4pF2 (03-JAN-08)
Donating Investigator	Leonard Shultz, The Jackson Laboratory


View larger image

Appearance
albino

Related Genotype: *A/A Tyr*^{c}*/Tyr*^{c}

Description
The NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice, commonly known as NOD scid gamma (NSG), do not express the *Prkdc* gene nor the X-linked *Il2rg* gene. NSG mice are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities. Histological examination of lymphoid tissues reveals absence of lymphoid cells and some cystic structures in the thymus, an absence of follicles in the spleen and markedly diminished celluarity of lymph nodes. NSG mice are deficient in mature lymphocytes, serum Ig is not detectable and natural killer (NK) cell cytotoxic activity is extremely low. These mice are resistant to lymphoma development even after sublethal irradiation treatment. These mutant mice have been shown to readily support engraftment of human CD34^{+} hematopoietic stem cells and represent a superior, long-lived model suitable for studies employing xenotransplantation strategies. Please note that the NSG carries the true null

interleukin-2 receptor gamma chain mutation and should not be confused with other strains that express a truncated interleukin-2 receptor gamma chain as described in: "Modulation of hematopoiesis in mice with a truncated mutant of the interleukin-2 receptor gamma chain" Ohbo K *et al. Blood* 1996. 87:956-67.

Development
These double mutant mice were produced by breeding female NOD.CB17-*Prkdc*^{scid}/J (Stock No. 001303) mice with male mice bearing the X-linked B6.129S4-*Il2rg*^{tm1Wjl}/J allele (Stock No. 003174). The resulting male mice heterozygous for the *Prkdc*^{scid} allele and hemizygous for the *Il2rg*^{tm1Wjl} allele were crossed to female NOD.CB17-*Prkdc*^{scid}/J (Stock No. 001303) mice for eight generations. Heterozygotes were interbred to produce mice homozygous for the *Prkdc*^{scid} allele and homozygous (females) or hemizygous (males) for the *Il2rg*^{tm1Wjl} allele.

Control Information

Control
001303 NOD.CB17-*Prkdc*^{scid}/J
001976 NOD/ShiLtJ

Considerations for Choosing Controls

Related Strains

Strains carrying *Il2rg*^{tm1Wjl} allele

003174 B6.129S4-*Il2rg*^{tm1Wjl}/J
003169 C.129S4-*Il2rg*^{tm1Wjl}/J
010636 NOD.Cg-*Prkdc*^{scid} *B2m*^{tm1Unc} *Il2rg*^{tm1Wjl}/SzJ
009617 NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl} Tg(HLA-A2.1)1Enge/SzJ
007799 NOD.Cg-*Rag1*^{tm1Mom} *Il2rg*^{tm1Wjl}/SzJ

View Strains carrying *Il2rg*^{tm1Wjl} (5 strains)

Strains carrying *Prkdc*^{scid} allele

001913 B6.CB17-*Prkdc*^{scid}/SzJ
001131 C3SnSmn.CB17-*Prkdc*^{scid}/J
002038 CB17;HPG-*Prkdc*^{scid} *Gnrh1*^{hpg}/Bm
001803 CBySmn.CB17-*Prkdc*^{scid}/J
004083 NOD.129(B6)-*Prkdc*^{scid} *Idua*^{tm1Clk}/J
001303 NOD.CB17-*Prkdc*^{scid}/J
002571 NOD.Cg *Prkdc*^{scid}-*B2m*^{b}/Dvs
004644 NOD.Cg *Prkdc*^{scid}-Tg(CSF2)2Ygy Tg(IL3)1Ygy Tg(KITLG)3Ygy/YgyJ
010636 NOD.Cg-*Prkdc*^{scid} *B2m*^{tm1Unc} *Il2rg*^{tm1Wjl}/SzJ
005345 NOD.Cg-*Cd38*^{tm1Lnd} *Prkdc*^{scid}/LtJ
006609 NOD.Cg-*Prkdc*^{scid} Tg(HLA-A2.1)1Enge/DvsJ
007840 NOD.Cg-*Prkdc*^{scid} Tg(Ins2-CD86)12B70Flv/FswJ
004262 NOD.Cg-*Prkdc*^{scid} Tg(HLA-A2.1)1Enge/Dvs
004346 NOD.Cg-*Prkdc*^{scid} Tg(Ins2-CD80)3B7Flv/DvsJ
004230 NOD.Cg-*Prkdc*^{scid} Tg(Ins2-E3)1Dvs/DvsJ
003843 NOD.Cg-*Prkdc*^{scid} Tg(Ins2-GAD2)1Lt/LtJ
003844 NOD.Cg-*Prkdc*^{scid} Tg(Ins2-GAD2)2Lt/LtJ
004257 NOD.Cg-*Prkdc*^{scid} Tg(TcrLCMV)327Sdz/Dvs
002570 NOD.Cg-*Prkdc*^{scid} *B2m*^{tm1Unc}/J
006605 NOD.Cg-*Prkdc*^{scid} *Emv30*^{b} Tg(HLA-A/H2-D/B2M)1Dvs/DvsJ
002313

NOD.Cg-*Prkdc*^{scid} *Emv30*^{b}/Dvs
005053 NOD.Cg-*Prkdc*^{scid} *Gusb*^{mps}/SndsJ
004606 NOD.Cg-*Prkdc*^{scid} *H2-Ab1*^{tm1Doi} Tg(HLA-DQA1,HLA-DQB1)1Dv/SzJ
005589 NOD.Cg-*Prkdc*^{scid} *H2-Ab1*^{tm1Doi}/SzJ
009617 NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl} Tg(HLA-A2.1)1Enge/SzJ
002380 NOD.Cg-Tg(Ins2-TAg)1Lt *Prkdc*^{scid}/DvsJ

View Strains carrying *Prkdc*^{scid} (26 strains)

Strains carrying other alleles of *Il2rg*

002479 STOCK *Il2rg*^{tm1Cgn}/J

View Strains carrying other alleles of *Il2rg* (1 strain)

Additional Web Information

Genetic Quality Control Annual Report
JAX® NOTES, Spring 2006; 501. Choosing an Immunodeficient Mouse Model.
JAX® NOTES, Spring 2008; 509. Jackson Laboratory's Leonard Shultz PhD Helps Develop a Better Leukemia Mouse Model.
JAX® NOTES, Spring 2009; 513. JAX-engineered NSG mouse, an innovative cancer research tool.
JAX® NOTES, Summer 2005; 498. NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/Sz, a New Model for Engraftment with Human Hematopoietic Stem Cells.
Strain-at-a-glance.

article discussing development of this strain

Phenotype

Phenotype Information

View Mammalian Phenotype Terms

Mammalian Phenotype Terms

assigned by genotype

***Il2rg*^{tm1Wjl}/*Il2rg*^{tm1Wjl} *Prkdc*^{scid}/*Prkdc*^{scid}**

NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/Sz

- **immune system phenotype**
- abnormal immune system organ morphology (MGI Ref ID J:109833)
  - lymph tissues are severely depleted of lymphoid cells
  - abnormal spleen B cell follicle morphology (MGI Ref ID J:109833)
    - spleens do not have detectable follicles
  - abnormal splenic cell ratio (MGI Ref ID J:109833)
    - two fold reduction in nucleated spleen cell numbers in comparison to Prkdc^{scid} controls
  - abnormal thymus morphology (MGI Ref ID J:109833)
    - thymus consists mostly of stromal cells with sporadic cyst structures
  - small lymph nodes (MGI Ref ID J:109833)
    - lymph nodes in the double mutant are markedly smaller than those of homozygous Prkdc^{scid} mice
    - lymph node hypoplasia (MGI Ref ID J:109833)
      - lymph nodes are hypocellular
- abnormal response to transplant (MGI Ref ID J:109833)